



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C12P 17/06, C07D 311/30, 311/62, C09K 15/06 // (C12P 17/06, C12R 1:785)</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/66062</b> <b>(43) International Publication Date:</b> 23 December 1999 (23.12.99)
<b>(21) International Application Number:</b> PCT/EP98/03736 <b>(22) International Filing Date:</b> 18 June 1998 (18.06.98) <b>(71) Applicants (for all designated States except US):</b> CONSIGLIO NAZIONALE DELLE RICERCHE [IT/IT]; P.le Aldo Moro, 7, I-00185 Roma (IT). RAO-ERBE DI RAO FELICE [IT/IT]; Via Bellini, 31, I-95027 S.Gregorio (IT). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> NICOLOSI, Giovanni [IT/IT]; Consiglio Nazionale delle Ricerche, Istituto per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico, Via del Santuario, 110, I-95028 Valverde (IT). PIATTELLI, Mario [IT/IT]; Consiglio Nazionale delle Ricerche, Istituto per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico, Via del Santuario, 110, I-95028 Valverde (IT). LAMBUSTA, Daniela [IT/IT]; Consiglio Nazionale delle Ricerche, Istituto per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico, Via del Santuario, 110, I-95028 Valverde (IT). PATTI, Angela [IT/IT]; Consiglio Nazionale delle Ricerche, Istituto per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico, Via del Santuario, 110, I-95028 Valverde (IT).		<b>(74) Agent:</b> SPADARO, Marco; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT). <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> BIOCATALYTIC PROCESS FOR THE PREPARATION OF 3-O-ACYL-FLAVONOIDS  <b>(57) Abstract</b> <p>The present invention provides a process for the preparation of 3 monoesters of flavonoids comprising the following steps: a) chemical esterification of flavonoid with an aliphatic acyl group having from 1 to 18 carbon atoms to give the corresponding peracetylated flavonoid, or, alternatively, partially acylated flavonoid; b) subsequent alcoholysis with an aliphatic alcohol having from 1 to 8 carbon atoms, in the presence of lipase from <i>Mucor miehei</i> in an organic solvent.</p>		

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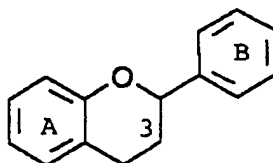
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BIOCATALYTIC PROCESS FOR THE PREPARATION OF 3-O-ACYL-  
FLAVONOIDS

Flavonoids are an important class of natural polyphenols present in various plants.

Many of them possess important biological activities, such as hepatoprotective, anticholesterolemic, antineoplastic, antiinflammatory, antiinfluenza, antiulcer, vasoprotective. Some flavonoids exploit inhibiting activity against tyrosine kinase and phosphatidyl-inositol kinase. Moreover, their antioxidant properties against peroxide radicals are comparable, if not greater, than conventional phenolic antioxidants. Many of these chemical and biological properties are strictly correlated to the position of hydroxyl groups on the flavane skeleton.



Flavane

Due to their polyhydroxylated nature flavonoids are insoluble in lipophilic media (oils and emulsions) and weakly bioavailable, so that their employment is limited.

It is necessary to develop a synthetic process to obtain selective esterification of hydroxyl group at the C-3 position, without involving the other phenolic groups in the molecule.

Regioselective alcoholysis of peracetylated flavonoids have been reported by Natoli et al. (Natoli, M; Nicolosi, G.; Piattelli, M, *J. Org. Chem.* 1992, 57, 5776-5778). The process described make use of *Pseudomonas*

*cepacia* lipase, which catalysed the alcoholysis of the acetoxyl group in different position, but not at C-3; nevertheless the 3-acetoxyl derivative is recovered in very low yield.

5       Lambusta e al., *Synthesis* 1993, 1155-1158 reported the preparation of (+)-3-O-acetylcatechin by alcoholysis of peracetylated (+)-catechin in the presence of *Pseudomonas cepacia* lipase, but the reaction conditions adopted are detrimental to the enzyme and consequently  
10 its fast inactivation is observed.

EP 0618203 reports catechins acylated at position C-3, prepared by esterifications of free catechin catalysed by *Streptomyces rachei* o *Aspergillus niger* carboxylesterase. Using this process authors enables for  
15 esters with acetyl, propyl and butyryl groups.

#### Summary of the Invention

It has now been found that it is possible to obtain 3-monoesters of flavonoid as the only reaction product by carrying out the alcoholysis of a peracylated flavonoid  
20 in organic solvent in the presence of *Mucor miehei* lipase.

Therefore, it is an an object of the present invention an efficient method of producing 3-monoesters of flavonoids, comprising:

- 25   a) chemical esterification of the flavonoid with an aliphatic acyl group having from 1 to 18 carbon atoms, to the corresponding peracylated flavonoid, or alternatively partially acylated flavonoid;
- 30   b) alcoholysis of the above ester with an aliphatic alcohol having from 1 to 8 carbon atoms or with a polyol in the presence of *Mucor miehei* lipase in an

organic solvent.

Advantageously, according to the process of the present invention, the lipase retains its catalytic activity for more process cycles

5        This invention also comprises new monoesters of flavonoids.

Detailed description of the invention

10        The lipase from *Mucor miehei* is well known since long time, but has never been employed in the esterification of phenols or hydrolysis of peracylated phenols.

According to the present invention, the alcoholysis of flavonoids, partially or exhaustively acylated, is carried out in an organic solvent.

15        Preferred examples of solvent can be aliphatic and aromatic hydrocarbons, halogenated hydrocarbons, ethers, more preferably *tert*-butyl methyl ether.

20        All the flavonoids possessing a hydroxyl function at the C-3 position can be used. Examples of such flavonoids are: quercetin, galangin, morin, fisetin, kampferolo, kampferide, (+)-catechin, (-)-catechin, (+)-epicatechin, (-)-epicatechin.

25        In a preferred embodiment, the process of the present invention provides the use of the lipase from *Mucor miehei* adsorbed on solid support, such as the commercially available Lipozyme<sup>®</sup> IM from Novo Nordisk or Chirazyme<sup>®</sup> L-9 from Boehringer Mannheim. Celite, or other usual supports, can be used too.

30        In a first embodiment of the present invention, the acylation of flavonoid is carried out by conventional procedures. For example, the acylating agent can be an

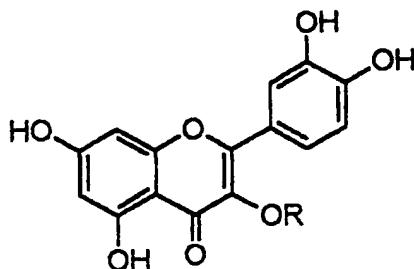
acyl halide, preferably acyl chloride. Examples of C<sub>2</sub>-C<sub>18</sub> aliphatic acyl group can be, in the context of this invention, acetyl, propionyl, butyryl, valeryl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, lauroyl, myristoyl, palmitoyl, heptadecanoyl, oleoyl, stearoyl. Palmitoyl is preferred.

The next step is an alcoholysis carried out in organic solvent using an aliphatic alcohol possessing from 1 to 8 carbon atoms, as above disclosed.

Examples of this aliphatic alcohol are methanol, ethanol, propanol, isopropanol, n-butanol, t-butanol, amyl alcohol, n-hexanol, n-octanol. n-Butanol is preferred. Examples of polyols are glycerine and glycols.

The product of interest, namely the flavonoid 3-monoester, is recovered from the reaction mixture by conventional procedures, well known to the person skilled in the art. By suitably selecting the acyl group and the aliphatic alcohol, the desired product can be recovered by cooling the reaction mixture.

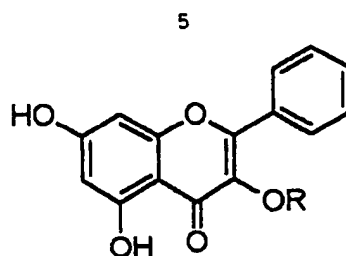
The process according to the present invention has produced new 3-monoesters of quercetin, as shown in formula 1:



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in which R is an acyl group of 3-18 carbon atoms.

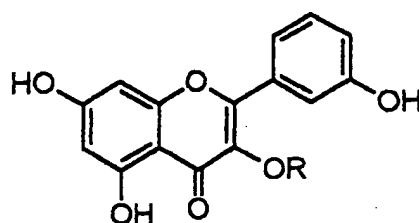
Of galangin, as shown in formula 2:



5

in which R is an acyl group of 3-18 carbon atoms.

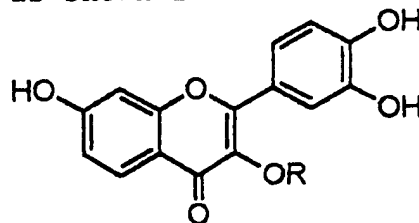
Of morin, as shown in formula 3:



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in which R is an acyl group of 2-18 carbon atoms.

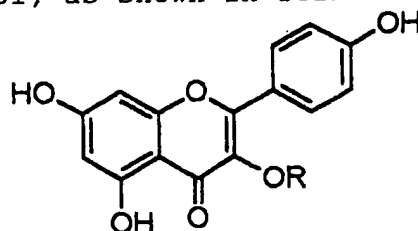
Of fisetin, as shown in formula 4:



20

in which R is an acyl group of 2-18 carbon atoms.

Of kaempferol, as shown in formula 5:

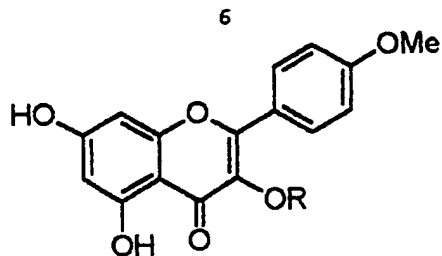


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in which R is an acyl group of 2-18 carbon atoms.

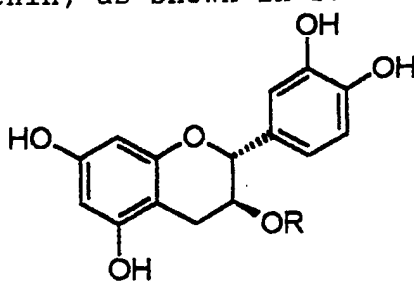
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Of kaempferide, as shown in formula 6:



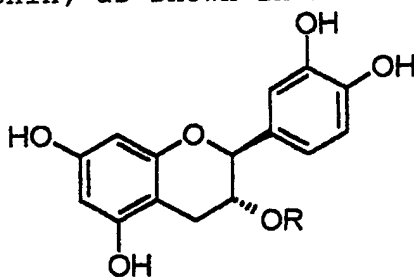
in which R is an acyl group of 2-18 carbon atoms.

Of (+)-catechin, as shown in formula 7:



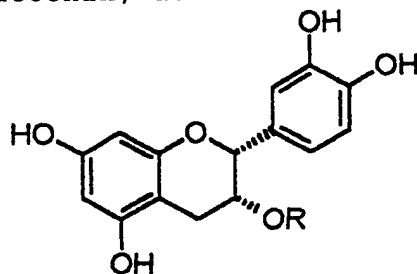
in which R is an acyl group of 2-18 carbon atoms.

Of (-)-catechin, as shown in formula 8:



in which R is an acyl group of 2-18 carbon atoms.

Of (-)-epicatechin, as shown in formula 9:

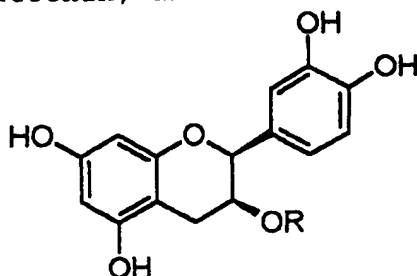


in which R is an acyl group of 2-18 carbon atoms.



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Of (+)-epicatechin, as shown in formula 10:



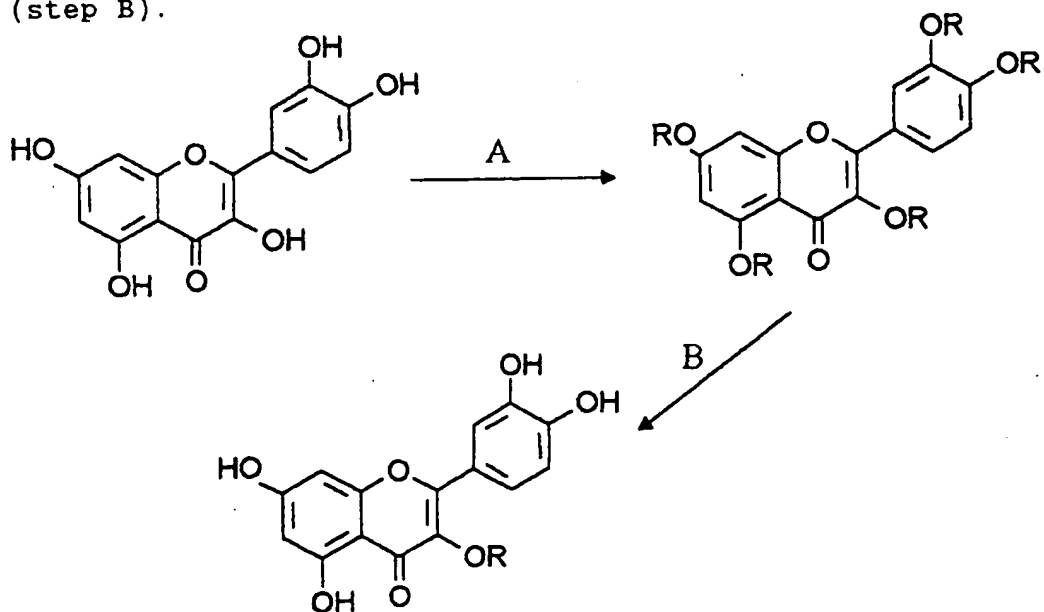
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in which R is an acyl group of 2-18 carbon atoms.

These compounds are useful as antioxidants.

To provide an example of the experimental process, the specific case of quercetin is reported here.

Quercetin (1) is esterified by a conventional chemical process using an aliphatic acyl group having 1-18 carbon atoms, to give the corresponding pentacyl derivative (step A). These esters are subjected to alcoholysis with an aliphatic alcohol, having from 1 to 8 carbon atoms, in the presence of *Mucor miehei* lipases (Lipozyme<sup>®</sup> IM, Chirazyme<sup>®</sup> L-9, or adsorbed on inert support) using tert-butyl methyl ether as the solvent (step B).



Alcoholysis leads to monoesters, in which all the phenolic hydroxyl functions are free, whereas the alcoholic group, at position C-3, remains esterified. It should be noted that the ester undergoing alcoholysis may have the hydroxyl groups on the A or B ring partially esterified. This is achieved by esterification with insufficient amounts of acylating agent or by a conventional protection process. Moreover, it is possible to use mixed esters in which hydroxyls in different positions are esterified by different acyls. In this way a number of advantages are realised. For example, alcoholysis of partial esters occurs faster. In the case of the mixed esters, if the desired 3-monoester possesses a long chain acyl group, it is advantageous to have all the other hydroxyls esterified with short chain acid groups, thus facilitating the conditions of the final alcoholysis.

The *Mucor miehei* lipase employed in immobilised form such as Lipozyme IM retains its activity throughout at least 10 cycles of use.

The use of lipases from porcine pancreas, *Pseudomonas cepacia*, *Chromobacterium viscosum*, *Candida cylindracea*, *Candida antarctica*, *Aspergillus niger*, *Rhizopus niveus*, *Rhizopus javanicus*, *Rhizopus delemar*, *Candida lipolitica*, *Penicillium roqueforti*, *Penicillium cyclopium* and esterase from porcine liver give scarce conversion or do not catalyse the alcoholysis at all.

The following example further illustrates the invention.

**30     Example:**

Quercetin (1 g, 3.3 mmol) was dissolved in t-butyl

methyl ether (50 mL) containing triethylamine (5 ml) and palmitoyl chloride (5.2 ml 7.2 mmol) was added at room temperature. After 12 hours the solution was acidified with dil. H<sub>2</sub>SO<sub>4</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> three times.  
5 The obtained organic phase was taken to dryness to furnish 4.75 grams of pentapalmitoyl quercetin (96% yield).

Lipozyme IM (2.5 grams) was added to a solution of tert-butyl methyl ether (250 ml) containing  
10 pentapalmitoyl quercetine (3 g, 2.9 mmol) and n-butanol (1 l, 10.9 mmol) and the suspension was shaken (300 rpm) at 45°C. After 5 days the reaction was stopped and the enzyme filtered off. The solvent was removed under vacuum and the residue added to hexane (200ml). On cooling the  
15 solution, 1 g of 3-O-palmitoylquercetin (92% yield) was obtained as a low-melting solid.

<sup>1</sup>H-nmr: <sup>1</sup>HNMR (CD<sub>3</sub>Cl<sub>3</sub>): δ 0.89 (bt, -CH<sub>3</sub>), 1.30 (bs, -(CH<sub>2</sub>)<sub>13</sub>-), 1.73 (bt, -CH<sub>2</sub>CO-), 6.31 (d, J= 2.2 Hz, H<sub>6</sub>), 6.55 (d, J= 2.2 Hz, H<sub>8</sub>), 7.02 (d, J= 8.2 Hz, H<sub>5'</sub>), 7.40  
20 (dd, J= 2.2, 8.2 Hz, H<sub>6'</sub>), 7.47 (d, J=2.2 Hz, H<sub>2'</sub>).

In the same way the following quercetin 3-monoesters have been prepared.

	Acyl group	R	Substrate	Product
			Quercetin	Quercetin
			Pentacylated	3-O-acylated
5	Acetyl	C <sub>2</sub> H <sub>3</sub> O	C <sub>25</sub> H <sub>20</sub> O <sub>12</sub>	C <sub>17</sub> H <sub>12</sub> O <sub>8</sub>
	Propionyl	C <sub>3</sub> H <sub>5</sub> O	C <sub>30</sub> H <sub>30</sub> O <sub>12</sub>	C <sub>18</sub> H <sub>14</sub> O <sub>8</sub>
	Butyryl	C <sub>4</sub> H <sub>7</sub> O	C <sub>35</sub> H <sub>40</sub> O <sub>12</sub>	C <sub>19</sub> H <sub>16</sub> O <sub>8</sub>
	Valeryl	C <sub>5</sub> H <sub>9</sub> O	C <sub>40</sub> H <sub>50</sub> O <sub>12</sub>	C <sub>20</sub> H <sub>18</sub> O <sub>8</sub>
	Hexanoyl	C <sub>6</sub> H <sub>11</sub> O	C <sub>45</sub> H <sub>60</sub> O <sub>12</sub>	C <sub>21</sub> H <sub>20</sub> O <sub>8</sub>
10	Heptanoyl	C <sub>7</sub> H <sub>13</sub> O	C <sub>50</sub> H <sub>70</sub> O <sub>12</sub>	C <sub>22</sub> H <sub>22</sub> O <sub>8</sub>
	Octanoyl	C <sub>8</sub> H <sub>15</sub> O	C <sub>55</sub> H <sub>80</sub> O <sub>12</sub>	C <sub>23</sub> H <sub>24</sub> O <sub>8</sub>
	Nonanoyl	C <sub>9</sub> H <sub>17</sub> O	C <sub>60</sub> H <sub>90</sub> O <sub>12</sub>	C <sub>24</sub> H <sub>26</sub> O <sub>8</sub>
	Decanoyl	C <sub>10</sub> H <sub>9</sub> O	C <sub>65</sub> H <sub>100</sub> O <sub>12</sub>	C <sub>25</sub> H <sub>28</sub> O <sub>8</sub>
	Lauroyl	C <sub>12</sub> H <sub>23</sub> O	C <sub>75</sub> H <sub>120</sub> O <sub>12</sub>	C <sub>27</sub> H <sub>32</sub> O <sub>8</sub>
15	Miristoyl	C <sub>14</sub> H <sub>27</sub> O	C <sub>85</sub> H <sub>140</sub> O <sub>12</sub>	C <sub>29</sub> H <sub>36</sub> O <sub>8</sub>
	Heptadeca- noyl	C <sub>17</sub> H <sub>33</sub> O	C <sub>100</sub> H <sub>170</sub> O <sub>12</sub>	C <sub>32</sub> H <sub>42</sub> O <sub>8</sub>
	Oleoyl	C <sub>18</sub> H <sub>33</sub> O	C <sub>105</sub> H <sub>170</sub> O <sub>12</sub>	C <sub>33</sub> H <sub>42</sub> O <sub>8</sub>
	Stearoyl	C <sub>18</sub> H <sub>35</sub> O	C <sub>105</sub> H <sub>180</sub> O <sub>12</sub>	C <sub>33</sub> H <sub>44</sub> O <sub>8</sub>

Claims

1. A process for the preparation of 3 monoesters of flavonoids comprising the following steps:
  - 5 a) chemical esterification of flavonoid with an aliphatic acyl group having from 1 to 18 carbon atoms to give the corresponding peracetylated flavonoid, or, alternatively, partially acylated flavonoid;
  - 10 b) subsequent alcoholysis with an aliphatic alcohol having from 1 to 8 carbon atoms, in the presence of lipase from *Mucor miehei* in an organic solvent.
2. A process according to claim 1, in which the flavonoid is selected from the group comprising  
15 quercetin, galangin, morin, fisetin, kampferolo, kampferide, (+)-catechin, (-)-catechin, (+)-epicatechin, (-)-epicatechin.
3. A process according to claims 1 or 2, in which the aliphatic acyl is selected from the group comprising  
20 acetyl, propionyl, butyryl, valeryl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, lauroyl, miristoyl, palmitoyl, heptadecanoyl, oleoyl, stearyl.
4. A process according to anyone of claims 1-3, in which the lipase from *Mucor miehei* is supported.
- 25 5. A process according to claim 4, in which the lipase is supported on celite.
6. A process according to anyone of claims 1-5, in which the solvent is a halogenated aliphatic hydrocarbon, an aromatic hydrocarbon, an ether.
- 30 7. A process according to claim 6, in which the solvent is tert-butyl methyl ether.

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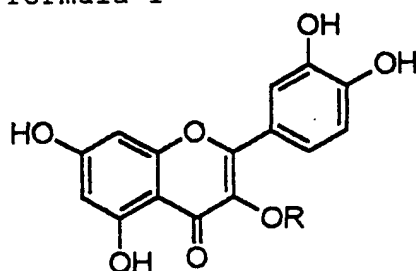
8. A process according to anyone of claims 1-7, in which, in step a) the esterification is partial and is performed with insufficient acylating agent.

9. A process according to anyone of claims 1-7, in which, in step a) the esterification is partial and is performed by previously protecting the hydroxyl groups and subsequentdeprotection.

10. A process according to anyone of claims 1-7, in which, in step a) the esterification is partial and is carried out in successive steps, with different acylating agents, to give mixed esters.

11. Compounds of formula 1

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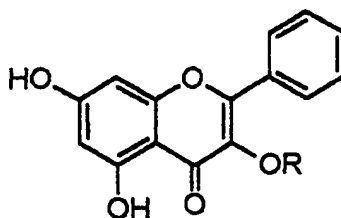
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in which R is an acyl group of 3-18 carbon atoms.

12. Compound according to claim 11, in which R is palmitoyl.

13. Compounds of formula 2;

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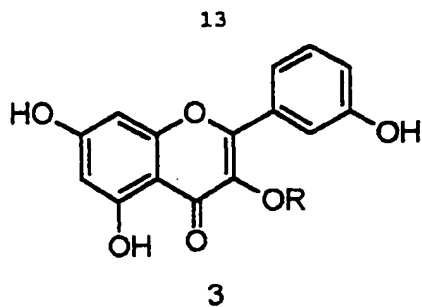


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in which R is an acyl group of 3-18 carbon atoms.

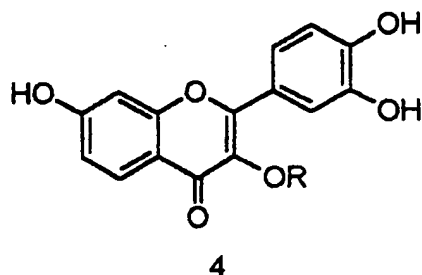
14. Compounds of formula 3;

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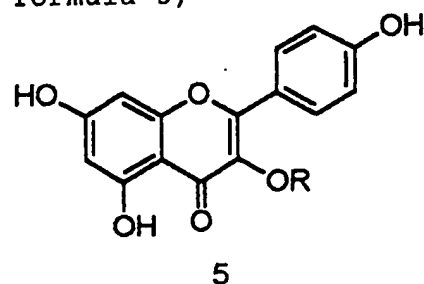
in which R is an acyl group of 2-18 carbon atoms.

15. Compounds of formula 4;



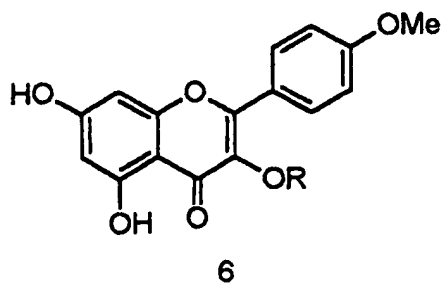
15 in which R is an acyl group of 2-18 carbon atoms.

16. Compounds of formula 5;



in which R is an acyl group of 2-18 carbon atoms.

25 17. Compounds of formula 6;

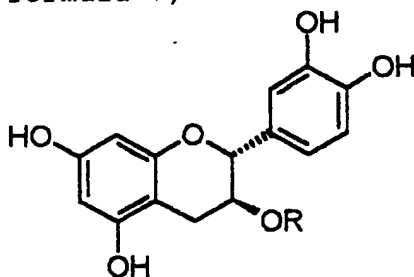


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in which R is an acyl group of 2-18 carbon atoms.

18. Compounds of formula 7;

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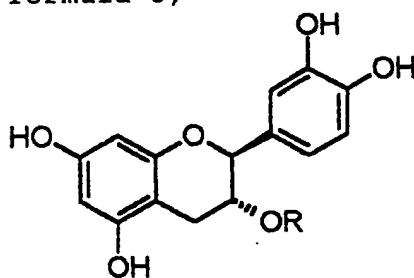
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in which R is an acyl group of 2-18 carbon atoms.

19. Compounds of formula 8;

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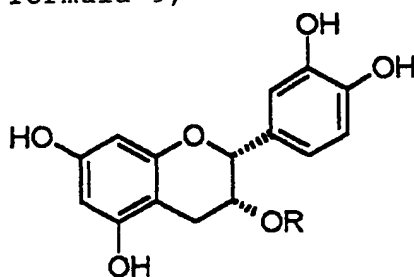


8

in which R is an acyl group of 2-18 carbon atoms.

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20. Compounds of formula 9;



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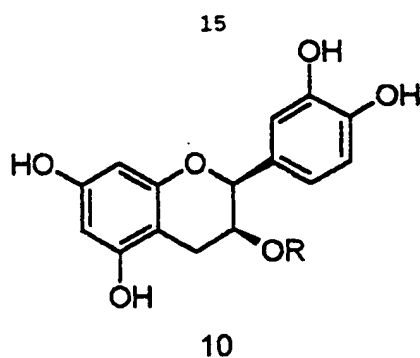
in which R is an acyl group of 2-18 carbon atoms.

21. Compounds of formula 10;

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5



in which R is an acyl group of 2-18 carbon atoms.

22. Use of the compounds of claims 11-21 as antioxidants.

# INTERNATIONAL SEARCH REPORT

Internal : Application No

PCT/EP 98/03736

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12P17/06 C07D311/30 C07D311/62 C09K15/06 //(C12P17/06,  
C12R1:785)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12P C07D C09K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 114, no. 11, 18 March 1991 Columbus, Ohio, US; abstract no. 101429, NATOLI, MARIAPINA ET AL: "Enzyme-catalyzed alcoholysis of flavone acetates in organic solvent" XP002093460 see abstract & TETRAHEDRON LETT. (1990), 31(50), 7371-4 CODEN: TELEAY;ISSN: 0040-4039,1990, --- -/--	1-10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

15 February 1999

Date of mailing of the international search report

26/02/1999

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## INTERNATIONAL SEARCH REPORT

Internat. J. Application No

PCT/EP 98/03736

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 124, no. 5, 29 January 1996 Columbus, Ohio, US; abstract no. 55331, OZEGOWSKI, RUEDIGER ET AL: "Enzymes in organic synthesis. 25. Lipase-catalyzed sequential esterification of (.+-)-2-methylbutanedioic anhydride - a biocatalytical access to an enantiomerically pure 1- monoester of (S)-2-methylbutanedioic acid" XP002093461 see abstract & LIEBIGS ANN. (1995), (9), 1699-702 CODEN: LANAEM; ISSN: 0947-3440, 1995, ---	1-10
X	LAMBUSTA, D. ET AL.: "Enzyme-Mediated Regioprotection-Deprotection of Hydroxyl-Groups in (+)-Catechin." SYNTHESIS, vol. 11, 1993, pages 1155-1158, XP002093458 cited in the application see the whole document ---	18
Y	---	1-10
X	NATOLI, M. ET AL.: "Regioselective Alcoholysis of Flavonoid Acetates with Lipase in an Organic Solvent." J. ORG. CHEM., vol. 57, no. 21, 1992, pages 5776-5778, XP002093459 cited in the application see the whole document ---	11, 17
Y	---	1-10
X	EP 0 618 203 A (MITSUI NORIN CO., LTD.) 5 October 1994 cited in the application see the whole document ---	19, 22
Y	---	1-10
X	CHEMICAL ABSTRACTS, vol. 99, no. 25, 19 December 1983 Columbus, Ohio, US; abstract no. 207106, SANSEI PHARMACEUTICAL CO. LTD., JAPAN: "Esters of fatty acids with quercetin as skin-whitening cosmetics" XP002093462 see abstract & JP 58 131911 A (SANSEI PHARMACEUTICAL CO. LTD., JAPAN) --- -/--	11-17

## INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/EP 98/03736

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 105, no. 1, 7 July 1986 Columbus, Ohio, US; abstract no. 3525, KULANTHAIVEL, PALANIAPPAN ET AL: "A new truxillate and some flavonoid esters from the leaf gum of Traversia baccharoides Hook f" XP002093463 see abstract & CAN. J. CHEM. (1986), 64(3), 514-19 CODEN: CJCHAG;ISSN: 0008-4042,1986, ---	11-17
X	CHEMICAL ABSTRACTS, vol. 105, no. 19, 10 November 1986 Columbus, Ohio, US; abstract no. 166411, PERRISSOUD, D. ET AL: "Inhibiting or potentiating effects of flavonoids on carbon tetrachloride-induced toxicity in isolated rat hepatocytes" XP002093464 see abstract & ARZNEIM.-FORSCH. (1986), 36(8), 1249-53 CODEN: ARZNAD;ISSN: 0004-4172,1986, ---	18-21
X	CHEMICAL ABSTRACTS, vol. 125, no. 25, 16 December 1996 Columbus, Ohio, US; abstract no. 320063, NANJO, FUMIO ET AL: "Scavenging effects of tea catechins and their derivatives on 1,1-diphenyl-2-picrylhydrazyl radical" XP002093465 see abstract & FREE RADICAL BIOL. MED. (1996), 21(6), 895-902 CODEN: FRBMEH;ISSN: 0891-5849, 1996, ---	18-21
X	CHEMICAL ABSTRACTS, vol. 120, no. 15, 11 April 1994 Columbus, Ohio, US; abstract no. 191378, TOBIASON, FRED L.: "MNDO and AM1 molecular orbital and molecular mechanics analyses of (+)-catechin, (-)-epicatechin, and their 3-O-acetyl derivatives" XP002093466 see abstract & BASIC LIFE SCI. (1992), 59(PLANT POLYPHENOLS), 459-78 CODEN: BLFSBY;ISSN: 0090-5542,1992, --- -/--	18-21

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Internati	Application No
PCT/EP 98/03736	

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHEMICAL ABSTRACTS, vol. 91, no. 21,  19 November 1979  Columbus, Ohio, US;  abstract no. 175201,  ZYMA S. A., SWITZ.: "O-Substituted  (+)-cyanidan-3-ols"  XP002093467  see abstract  &amp; JP 54 081274 A (ZYMA S. A., SWITZ.)  -----</p>	18-21

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat. Application No

PCT/EP 98/03736

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0618203 A	05-10-1994	JP 6279430 A	04-10-1994